AMENDMENT

IN THE CLAIMS: Please cancel claims 1-18, without prejudice.

REMARKS

Applicants have carefully studied the Office Action mailed on March 29, 2002, which issued in connection with the above-identified application. The present amendments and remarks are intended to be fully responsive to all points of rejection raised by the Examiner and are believed to place the claims in condition for allowance. Favorable reconsideration and allowance of the present claims are respectfully requested.

Pending Claims

Claims 1-25 were pending and at issue in the application. In the Action, claims 13-16 and 19-25 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite; claims 1-25 have been rejected under the judicially created doctrine of obviousness-type double patenting; claims 1, 2, 5, 6, and 8-9 have been rejected under 35 U.S.C. §102(b) as being anticipated by the prior art; claims 1-25 have been rejected under 35 U.S.C. §103(a) as being obvious over the prior art.

Claims 1-18 have been canceled. Following entry of this amendment, claims 19-25 will be pending.

Obviousness-type Double Patenting

In the Action, claims 1-25 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-51 of the commonly owned U.S. Patent No. 6,333,044. As claims 1-18 have been canceled, the rejection of these

claims is rendered moot. With respect to the remaining claims, applicants note that, pursuant to the Examiner's request, a Terminal Disclaimer is attached herein as Exhibit A. This Terminal Disclaimer is being submitted as an expedient and no admission is hereby made or intended regarding the patentability of the claims of the '044 patent.

35 U.S.C. §112, Second Paragraph, Rejections

In the Office Action, claims 13-16 and 19-25 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As claims 13-16 have been canceled, the rejection of these claims is rendered moot.

The Examiner states that claims 19, 20 and 25 are indefinite in their recitation of the term "ketorolac-based" and the trademark/trade name KETOROLAC™. Applicants respectfully traverse the rejection and note that the present claims recite "ketorolac" and not "KETOROLAC™". In contrast to the Examiner's assertion, ketorolac is not a trademark. As follows from the attached printout from Electronic Orange Book of Approved Drug Products (Exhibit C), ketorolac is an active ingredient in a range of pharmaceuticals having different proprietary names. As shown on the last page of the printout, such proprietary name in the case of preparations produced by SYNTEX (USA) INC. is TORADOL. *See* also a printout from ChemFinder.com (attached as Exhibit D).

In light of the foregoing arguments and amendments, it is respectfully submitted that the rejection of claims based upon 35 U.S.C. §112, second paragraph, is overcome and withdrawal of such is kindly requested.

35 U.S.C. §102(b) Rejection

In the Office Action, claims 1, 2, 5, 6, and 8-9 stand rejected under 35 U.S.C. §102(b) as being anticipated by Muchowski *et al.* (U.S. Patent No. 4,089,969). As claims 1, 2, 5, 6, and 8-9 have been canceled, the rejection of these claims is rendered moot.

35 U.S.C. §103(a) Rejections

The Examiner has also rejected claims 1-25 under 35 U.S.C. §103(a) as being obvious over Muchowski *et al.* (U.S. Patent No. 4,089,969) in view of the Abstract of the Japanese Patent Publication No. JP 03-072433 (full-text English language translation is attached as Exhibit B) and Cetenko *et al.* (U.S. Patent No. 4,943,587). The Examiner contends that (i) JP 03-072433 supplements the disclosure of the primary reference by describing a foam aerosol comprising 0.2-5% (by weight) of a non-steroidal analgesic and (ii) the Cetenko *et al.* patent supplements the disclosure of the primary reference by teaching intranasal administration of non-steroidal anti-inflammatory drugs (NSAIDs) such as hydroxamic acid derivatives of ketorolac in the form of sprayable formulations. The Examiner concludes that it would have been obvious to have modified the method of administering ketorolac compositions taught by Muchowski *et al.* for the treatment of pain and inflammation by using the aerosolized intranasal formulations as taught by JP 03-072433 and Cetenko *et al.*

As claims 1-18 have been canceled, the rejection of these claims is rendered moot. With respect to the remaining claims, the rejection is respectfully traversed for reasons set forth hereinafter. While applicants agree with the Examiner's summary of the factual inquiry set forth in *Graham v. John Deere*, applicants disagree with the application of the art to the claims under consideration.

It is respectfully submitted that the differences between the prior art and the claims at issue are such that the claimed subject matter would not have been obvious to one of ordinary skill in the art. It is well established that there must be some motivation to combine

references in a way that suggests doing what the inventors have done to make the claimed subject matter obvious. In this particular case, there is no motivation to combine the references, and even if the references are combined there is no suggestion of the claimed invention.

In considering obviousness, both the suggestion of making the present invention, and a reasonable expectation of success must be found in the prior art, not in the applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 U.S.P.Q.2nd 1529, 1531 (Fed. Cir. 1988); MPEP Section 2143. Applicants respectfully submit that neither of these criteria has been met. In contrast to the Examiner's assertion, there is neither a suggestion nor a motivation in the references of record to combine them to produce a pharmaceutical nasal spray comprising a systemically effective amount of a ketorolac-based analgesic as recited in the present claims.

The Examiner has chosen from the entire universe of references the three that he believes make the claimed invention obvious. It would be presumed, however, that one of ordinary skill would be aware not only of the cited references, but also of other references needed to interpret the references and the application in a reasonable way, and would have enough experience and education to understand the invention and the prior art.

With respect to Muchowski *et al.*, applicants respectfully note that this patent was applied by the Examiner against the claims of the parent application Serial No. 07/875,700 (*see* Office Action dated July 29, 1992; paper No. 4) and was successfully overcome by the applicants (*see* the Response to the Office Action dated October 19, 1992; paper No. 5, copy attached as Exhibit E). The Muchowski *et al.* patent does not disclose or suggest (and even teaches away from) the pharmaceutical nasal spray comprising a systemically effective amount of a ketorolac-based analgesic as recited in the present claims. In fact, as acknowledged by the Examiner in the last paragraph at page 4 of the Office Action, Muchowski *et al.* patent, which incidentally is the basic patent for ketorolac (owned by SYNTEX (USA) INC., the original developer and marketer of this drug), is totally silent with respect to intranasal administration. The importance of ketorolac was obviously recognized at the time the Muchowski *et al.* patent was applied for and a diligent effort was made by Muchowski to disclose every dosage form and

method of administration that was then thought possible. Thus, as stated in column 9, lines 25-31 of this patent: "administration can be for example, orally, parenterally or topically, in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, solutions, suspensions, emulsions, creams, lotions, ointments or the like, preferably in unit dosage forms suitable for simple administration of precise dosages." The absence of intranasal dosage forms is noted. Column 9, line 19 - column 10, line 14 describes in detail oral and suppository dosage forms, and mentions liquid dosage forms, but the intranasal dosage forms are again conspicuously absent. Column 11, lines 35-67, describes additional dosage forms such as oral tablets, vaginal tablets, uterine tablets, suppositories, pills, capsules, and liquid solutions and suspensions for oral and parenteral use. Again, intranasal dosage forms are neither mentioned, nor suggested.

Applicants respectfully note that the property of being suitable for administration through the intranasal mucosa cannot be considered inherently present in the dosage forms disclosed in Muchowski *et al.* patent. As stated in MPEP 2112, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ 2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ 2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

The analysis of the case law on the subject of inherency demonstrates that the Examiner has not established a *prima facie* case of obviousness. Thus, that the prior art product may possibly have the same features as the claimed invention will not substantiate a finding of inherency. Rather, inherency must flow as a necessary conclusion from the prior art, not simply a possible one. *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however may not be established by probabilities or

possibilities. *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q. 2d 1949, 1950-51 (Fed. Cir. 1999).

Importantly, Muchowski *et al.* patent is not only silent with respect to but also teaches away from the pharmaceutical nasal spray comprising a systemically effective amount of a ketorolac-based analgesic of the present invention. Thus, Example 43 of this patent describes a ketorolac composition containing a variety of ingredients that are unsuitable for intranasal administration, such as fumaric acid, sorbitol, Veegum, flavoring, and coloring. Furthermore, Example 41 of the patent discloses an injectable solution of ketorolac containing 10 mg/ml of active ingredient, *i.e.*, 1%. In contrast to the nasal spray recited in the present claims and disclosed in the instant application, which contains 5-20% (weight/volume), preferably 15%, of active ingredient, this solution does not contain enough concentration of ketorolac to be systemically effective if intranasally administered (*i.e.*, if intranasal administration of this parenteral solution were attempted, it would not result in an effective amount of ketorolac being released in the bloodstream). If this solution containing 1% ketorolac were sprayed to the nose of a patient, so many "puffs" would be necessary to deliver enough ketorolac to the nose, that the total amount of liquid would exceed the capacity of the nose to hold it and/or would be quickly cleared from the mucosa and thus be ineffective.

In contrast to the Examiner's assertion, the secondary references do not cure the deficiency of the primary reference. Applicants respectfully submit that, similarly to Muchowski *et al.*, JP 03-072433 does not disclose or suggest (and even teaches away from) the pharmaceutical nasal spray comprising a systemically effective amount of a ketorolac-based analgesic as recited in the present claims. JP 03-072433 discloses foamy aerosol preparations for external and not for intranasal administration. As specified at page 14 of the attached translation, these preparations are designed to be well absorbed through the skin and are useful in orthopedic field "as a treatment for inflammatory ailments such as muscle pain, back pain, joint pain, bruising, spraining, inflammation of the tendon and the like". In this patent, the term "nasal" arises only in connection with the unwanted side-effect of aerosol administration, *i.e.*, nasal irritation. As demonstrated in Test 1 and discussed in the section "(5) Advantages of the invention" (pages 12-14 of the translation), these foamy aerosol preparations produce small

bubbles which do not burst and therefore do not reach the nasal mucous membrane (to cause its irritation), when sprayed on the surface of the skin. JP 03-072433 further teaches away from using the aerosol preparations intranasally by disclosing that these preparations contain concentrations of active ingredients, which are in the range of 0.2-5% (*see* last paragraph at page 4 of the translation) and are therefore below the level optimal for systemic intranasal administration (compare to 5-20% recited in the present claims). Also, JP 03-072433 teaches away from the intranasal administration of the aerosol preparations by disclosing various agents and/or additives, which, if sprayed directly on the nasal mucous membrane, would cause its irritation. For example, as disclosed in the second paragraph at page 6 of the translation, such additives can include powders (*e.g.*, talc, silicon powder, nylon powder), wetting agents (*e.g.*, propylene glycol, 1,3-butylene glycol, 3-methyl-1,3-butane diol), ethanol, isopropanol, and the like. Applicants also note that, although ketorolac is included in the long "laundry list" of NSAIDs useful in the preparations disclosed in JP 03-072433 (*see, e.g.*, claim 3), there is no specific disclosure, example, or suggestion with respect to ketorolac. The patent provides specific disclosure only with respect to ketoprofen, felbinac, indomethacin, and loxoprofen, all of which are structurally and pharmacologically unrelated to ketorolac.

Applicants respectfully submit that Cetenko *et al.* patent also does not supplement the disclosure and does not cure the deficiency of the other two cited references. As correctly noted by the Examiner in the last paragraph at page 6 of the Office Action, Cetenko *et al.* disclose intranasally administrable compositions containing hydroxamic acid derivatives of acyl residues of a number of different NSAIDs, including ketorolac, but do not disclose or suggest compositions containing 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, optically active forms thereof or pharmaceutically acceptable salts thereof, as recited in the present claims. It is respectfully noted that, although these drugs and the drugs recited in the present claims belong to the same group of non-steroidal anti-analgesics (NSAIDs), they are different not only in their chemical structure but also in their pharmaceutical and functional properties.

Thus, it is well established in the field of pharmacology that the major mechanism of action of NSAIDs is the inhibition of cyclooxygenase (COX), the enzyme participating in the conversion of arachidonic acid into prostaglandins. The two isoforms of COX, inducible COX-2

and constitutive COX-1, are responsible for some aspects of pain/inflammation and for most of the gastro-protective prostaglandin synthesis in the stomach/duodenum, respectively (*see, e.g.*, a recent review by Steinmeyer, Arthritis Res., 2000, 2:379-385, attached as Exhibit F). It has been also shown that NSAIDs may function by inhibiting 5-lipoxygenase (LOX), an enzyme participating in the convertion of arachidonic acid into leukotrienes (*see, e.g.*, Abstract of Fiorucci *et al.*, Biochem. Pharmacol., 2001, 62:1433-1438, attached as Exhibit G). Ketorolac (*i.e.*, 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid and pharmaceutically acceptable salts thereof) is a known potent COX-1/COX-2 inhibitor (*see, e.g.*, Jett *et al.*, J. Pharmacol. Exp. Ther., 1999, 288:1288-1297, attached as Exhibit H). As demonstrated by Handley *et al.* (J. Clin. Pharmacol., 1998, 38:25S-35S, attached as Exhibit I), at concentrations at which it efficiently inhibits COX, ketorolac does not inhibit LOX (*see, e.g.*, Table II at page 29S). In contrast, as specified in column 4, lines 34-55, column 18, lines 26-47, column 29, Table 2, and claims 10-11 of Cetenko *et al.* patent, the disclosed hydroxamic acid derivatives of NSAIDs are dual COX/LOX inhibitors. The data presented in Table 2 (column 29) clearly demonstrate that the extent of the COX/LOX inhibitory activity for different hydroxamic acid derivatives and for different NSAIDs varies widely and is rather unpredictable.

In view of the total absence of disclosure with respect to specific hydroxamic acid derivatives of ketorolac in Cetenko *et al.* patent, applicants respectfully submit that the state of the art at the time the cited references and the parent of the present application were filed was such that a possibility for intranasal administration of any given drug could not be predicted on the basis of data for any other structurally unrelated drug. For example, Hussain *et al.* patent (U.S. Patent No. 4,885,287) cited in the Information Disclosure Statement (IDS) and filed in August, 1988 states in column 2, lines 22-38 that the success of intranasal administration for various drugs is unpredictable and that other medications (none of which are NSAIDs) have been administered with varying degrees of success. This implies that, at best, nasal delivery of drugs is experimental, *i.e.*, some compounds could succeed, but some will fail. This unpredictability is further supported by U.S. Patent No. 4,778,810 (cited in the IDS submitted concurrently with this application), which recites in column 2, lines 9-14 that "while nasal administration ... is known, it is not a necessary conclusion ... that all therapeutic agents can be usefully administered

by this route. In fact ... many drugs cannot be administered by the nasal route." *See* also page 2, second paragraph of the reference by Y.W. Chien and S.F. Chang (cited in the IDS). Similarly, as summarized at page 3, line 31 - page 4, line 12 of the instant specification: "Although nasal administration to mammals (especially humans) of certain therapeutic agents is known, it is not to be presumed that all therapeutic agents can be effectively administered by this route. To the contrary, many therapeutic agents cannot be nasally administered... The ability of drug molecules to be absorbed by the nasal mucous membranes is utterly unpredictable, as is the ability of intranasal formulations to avoid irritation of the mucous nasal membranes." It follows, that, in contrast to the Examiner's assertion, this Cetenko *et al.* patent does not contain any suggestion or motivation to use ketorolac (*i.e.*, 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, optically active forms thereof or pharmaceutically acceptable salts thereof) in the intranasal sprays recited in the present claims.

In light of the foregoing arguments, it is respectfully submitted that the instant claims are not anticipated by or obvious over the cited art. Reconsideration and withdrawal of the rejections based upon 35 U.S.C. §102(b) and 103(a) is believed to be in order.

SUBMISSION OF THE FULL-TEXT TRANSLATION OF JP 03-072433

As specified above, applicants submit herewith a duplicate copy of the full-text English language translation of the Japanese Laid-Open Patent Publication No. JP 03-072433 (attached as Exhibit B). This translation is being submitted in compliance with 37 C.F.R. §1.56, but is not to be construed as an admission that such document is relevant as prior art. The translation was made on September 18, 2002, *i.e.*, less than three months before the filing of this response. Accordingly, no fee is believed to be due. However, if the Examiner, believes otherwise, he is authorized to charge any additional fees required in connection with this submission to our Deposit Account No. 04-0100.

CONCLUSION

Applicants request entry of the foregoing amendments and remarks in the file history of this application. In view of the above amendments and remarks, it is respectfully submitted that claims 19-25 are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned attorney at (212) 527-7727. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

Respectfully submitted,

Dated: September 30, 2002

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